The term "bioequivalent" means that a test drug product provides similar bioavailability compared to a reference listed drug product pursuant to the criteria set forth for bioequivalence by the United States Food and Drug Administration, as amended.

The term "bio-identical hormones", as used herein, means those synthetically-derived compounds which are identical in chemical structure to the hormones naturally produced in vivo. These natural or bio-identical hormones are synthesized from various ingredients to match the chemical structure and effect of estradiol or estrone, or estriol (the 3 primary estrogens).

The term, "C_{max}" as used herein, refers to the maximum value of blood concentration shown on the curve that represents changes in blood concentrations of estradiol and/or estrone over time.

The term "co-administered" as used herein, means that two drug products are administered simultaneously or sequentially on the same or different days.

The term "drug product" as used herein means at least one active pharmaceutical ingredient in combination with at least one excipient and provided in unit dosage form.

The term "excipients," as used herein, refer to non-active pharmaceutical ingredients such as carriers, solubilizing agents, oils, lubricants and others used in formulating pharmaceutical products. They are generally safe for administering to animals, including humans, according to established governmental standards, including those promulgated by the United States Food and Drug Administration.

The term "natural," as used herein with reference to hormones discussed herein, means bio-identical hormones synthesized to match the chemical structure and effect of those that occur naturally in the human body (endogenous). An exemplary natural estrogen is estradiol (also described as 17β-estradiol and E2).

The term "medium chain," as used herein means any medium chain carbon-containing substance, including C4-C18, and including C6-C12 substances, fatty acid esters of glycerol, fatty acids, and mono-, di-, and tri-glycerides of such substances.

The term "reference listed drug" as used herein means VAGIFEM.

The term "solubilizer," as used herein, means any substance or mixture of substances that may be used to enhance the solubility of estradiol, including, for example and without limitation, appropriate pharmaceutically acceptable excipients, such as solvents, co-solvents, surfactants, emulsifiers, oils and carriers.

The term "treatment", as used herein, or a derivative thereof, contemplates partial or complete inhibition of the stated disease state or condition when a formulation as described herein is administered prophylactically or following the onset of the disease state for which such formulation is administered. For the purposes of the present disclosure, "prophylaxis" refers to administration of the active ingredient(s) to an animal, typically a human, to protect the animal from any of the disorders set forth herein, as well as others.

The term, "Tmax" as used herein, refers to the time that it takes for estradiol and/or estrone blood concentrations to reach the maximum value.

Description

Provided herein are pharmaceutical formulations comprising solubilized estradiol; providing said formulations do not embrace within the fill one or more of the following components: a hydrophilic gel-forming bioadhesive agent; a lipophilic agent; a gelling agent for the lipophilic agent, and/or a hydrodispersible agent. The hydrophilic gel-forming bioadhesive agent may provide or exclude one or more of a: carboxyvinylic acid; hydroxypropylcellulose; carboxymethylcellulose; gelatin; xanthane gum; guar gum; aluminum silicate; or mixtures thereof. The lipophilic agent may provide or exclude one or more of a: liquid triglyceride; solid triglyceride (with a melting point of about 35° C.); carnauba wax; cocoa butter; or mixtures thereof. The gelling agent may provide or exclude one or more of a hydrophobic colloidal silica. The hydrodispersible agent may provide or exclude one or more of a: polyoxyethylene glycol; polyoxyethylene glycol 7-glyceryl-cocoate and mixtures thereof.

Generally, the pharmaceutical formulations described herein are prepared and administered as filled capsules, typically soft capsules of one or more materials well known in the art including, for example and without limitation, soft gelatin capsules. However, in various embodiments, pharmaceutical formulations described herein are prepared as a gel, cream, ointment, transdermal delivery system or like preparation.

Other aspects of the present disclosure include the use of formulations as described herein for the treatment of vulvovaginal atrophy including the treatment of at least one VVA symptom including, for example and without limitation, dryness, itching, soreness, irritation, bleeding and dyspareunia.

Another aspect of the present disclosure provides uses of the formulations described herein for the treatment of estrogen-deficient urinary states.

Another aspect of the present disclosure provides alcohol-free or substantially alcohol-free formulations, and uses thereof. Among others, the formulations offer improved comfort during use, thus tending to enhance patient compliance.

The methods of treatment described herein are generally administered to a human female.

A further aspect of the present invention provides formulations of the present invention wherein circulating blood level concentrations following administration of a formulation of the present invention are bioequivalent to circulating blood level concentrations following administration of the reference listed drug product, as determined through the completion of a bioequivalence clinical study.

The formulations of the present disclosure may also be vaginally administered with or without the co-administration of an orally administered estrogen-based pharmaceutical drug product, or patch, cream, gel, spray, transdermal delivery system or other parenterally-administered estrogen-based pharmaceutical drug product, each of which can include natural, bio-similar, or other synthetic or derived estrogens and/or an administered progestin. As used herein, the term "progestin" means any natural or man-made substance that has properties similar to progesterone.

Modulation of circulating estrogen levels provided via the administration of a formulation of the present disclosure, if any, are not intended to be additive to any co-administered estrogen product and its associated circulating blood levels.

The timing of administration of a formulation of the present disclosure may be conducted by any safe means as prescribed by an attending physician. Typically, a patient will insert one capsule intra-vaginally each day for 14 days, then one capsule twice weekly for the remaining time prescribed by such physician. Intra-vaginal insertion may be via the use of an applicator or without an applicator via use of the patient's digits. Use of an applicator or otherwise requires due care as to not puncture or tear surrounding tissue.

Estradiol dosage strengths can vary. For formulations of the present disclosure, estradiol (or estradiol equivalent to the extent such estradiol is in a hydrated or other form requiring compensation therefore) dosage strength of is at least about 1